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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,378	12/27/2001	Walter Muller	512100-2024	6397

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EXAMINER	
GHALI, ISIS A D	

ART UNIT	PAPER NUMBER
1615	5

DATE MAILED: 05/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,378	MULLER, WALTER	
	Examiner	Art Unit	
	Isis Ghali	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The receipt is acknowledged of applicant's priority document and IDS, both filed 12/27/2001.

Claim Objections

1. Claims 4-9 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n).

2. Claim 7 objected to because of the following informalities: beside the multiple dependency of the claim, the claim depends on it self. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, component (c) recites the limitation "the solvent" in the claim. There is insufficient antecedent basis for this limitation in the claim.

Furthermore, claim 1, component (a), applicant recites polysiloxanes in general, and later in component (d) applicant recites only one polysiloxane in which the solvent is soluble, and the examiner is wondering which particular polysolixane applicant intends to specify to dissolve the solvent.

Regarding claims 1, 6, 7, 8, and 10, a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The claims are rendered indefinite by raising a question or doubt introduced by the limitations following the expression "preferably" because it is subject of more than one interpretation, and one interpretation would render the claim unpatentable over the prior art. In the present instance, claim 1 recites the broad recitations "at least 70% of polysiloxane" and "at least 50% of solvent", and the claim also recites "preferably at least 80% of polysiloxane" and "preferably at least 80% of the solvent" which are the narrower statements of the range/limitation. Claim 6 recites the broad recitations "ambiphilic solvent", and the claim also recites "preferably diethylene glycol monoethyl ether, etc." which are the narrower statements of the range/limitation. Claim 7 recites the broad recitations "judiciously at least 10^0 C", and the claim also recites "preferably at least 30^0 C" which is the narrower statements of the range/limitation. Claim 8 recites the broad recitations "5-50 micron", and the claim also recites "preferably 5-30" which is the narrower statements of the range/limitation.

Claim 10 recites the broad recitations "temperature between 25 and 100^0 C", and the claim also recites "preferably between 30 and 80^0 C" which is the narrower statements of the range/limitation. For examination purposes, the claims are given the broadest interpretation as follows: polysiloxane forms at least 70% of the polymer in the polymer matrix; the ambiphilic solvent forms at least 50% of the solvent for the active substance; the solvent is an ambiphilic solvent in general; the boiling point is at least 10^0C above; the microreservoir diameter is 5-50 micron; and the temperature of removing the solvent is between 25 and100^0 C.

The present claim 1 is directed to a transdermal therapeutic system (TTS) comprising an impermeable backing layer and a protective liner; at least one polymer layer with microreservoirs containing at least one active substance in dissolved form. The polymer layer comprises polymer that contains at least 70% by weight of polysiloxane. The solvent for the active substance contains at least 50% by weight of ambiphilic solvent, and component (d) of the claim recites physiochemical properties of the solvent.

Claim 2 recites that the polysiloxane is amine-resistant.

Claim 3 recites that the microreservoirs are essentially free from water.

Claim 4 recites that the polysiloxane is self-adhesive, and filler that is interpreted by the examiner as part of the TTS as a whole and not a component of the polysiloxane, and it is only optional.

Claim 5, recites the TTS further comprising a self-adhesive layer to anchor to the skin or to the backing layer.

Claim 6 recites the preferred ambiphilic solvents and their physical properties (liquid at room temperature, and boiling point more than 80^0 C under standard conditions).

Claim 7 recites that the boiling point of the dipolar solvent is above that of the solvent for the polysiloxane by at least 10^0C.

Claim 8 recites the diameters of the microreservoirs to be from 5 to 50 micrometer and does not exceed the 80% of the thickness of the polymer layer.

Claim 9 recites the microreservoirs further comprise crystallization inhibitor, viscosity increasing agent and/or pH regulator.

Claim 10 recites a process for making the TTS comprising dissolving the active substance in the ambiphilic solvent, dispersing the resulting solution in a polysiloxane solution, coating the resulting dispersion onto a film, and removing the solvent of the polysiloxane at temperature between 25 to 100^0 C.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 3-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 87/07138 ('138) in view of US 5,071,657 ('657).

WO '138 teaches a transdermal absorption dosage unit comprising substantially impervious backing layer, a layer of polymer matrix in which a drug is microdispersed (reads on microreservoirs); an adhesive means for securing the dosage unit to the skin of the treated subject; and a release liner (abstract; page 19, line 25; page 35, lines 1-40). The polymer matrix is made from polysiloxane polymer or polydimethylsiloxane, applicant claims polysiloxanes in general (page 5, lines 24-31; page 36, lines 10-12). The pharmaceutical agents are dissolved in a selected solvent (page 16, lines 51-56). The amount of the solvent is between 0 - 50% by weight of the polymer matrix (page 16, lines 14-21). The polydimethylsiloxane polymer forms 70 parts of the polymer matrix (page 17, lines 25-31). Thus, the amounts of the solvent and polysiloxane polymers are met by the reference. The thickness of the polymer matrix layer is 0.05 mm to 5 mm (50-5000 micron), and the microdispersed compartments (microreservoirs) have cross-sectional dimensions of 10-200 micron (page 17, lines 50-56; page 36, lines 45-53).

Thus, the maximum size of the microreservoirs (200 micron) does not exceed 80% of the thickness of the polymer matrix layer (that can be up to 4000 micron), and this meets the limitation of claim 8. The reference disclosed a process for the manufacture of the polymer matrix that includes dissolving and dispersing the drug in the solvent, and then mixing the dispersion with the polysiloxane polymer to form microdispersion, then heating to temperature of 20^0 C 100^0 C to form the polymer sheet that can be formed directly on the backing sheet (page 16, lines 50-56; page 17, lines 1-6, 40-51; page 18, lines 6-10). This method of manufacture does not include water and that means that the microreservoirs will be essentially free from water, and that meets the limitation of claim 3. It is expected for the polysiloxane polymer to have the same physical properties such as adhesiveness, and that meets claim 4 because the filler recited in claim 4 is only an optional component.

The reference, however, does not teach specifically the ambiphilic solvents and their physical properties (as recited in component (c) and (d) of claims I, and claims 6 and 7), and does not teach that the microreservoirs comprise crystallization inhibitor, viscosity increasing agent and/or pH regulator (claim 9).

US '657 teaches a device for transdermal administration of active medicinal agent dissolved in a nonflowable gel that form microdispersion (microreservoirs) in a silicone elastomer (abstract). The nonflowable gel comprises a thickener, i.e. viscosity increasing agent (claim 9), and solvent that has boiling point of 80^0 C or higher (col.2, lines 41-45). These solvents include propylene glycol, and diethylene glycol and ethers thereof, i.e. ambiphilic solvents claimed in claims 1 (c) and 6 (col.2, lines 53-57). It is

expected that the solvents disclosed by the reference would have the same physical properties as claimed by applicant in claims 1 (d), 6 and 7, i.e. solubility in polysiloxane, miscibility with water, being in liquid state at room temperature and having higher boiling point than the boiling point of the solvent for the polysiloxane. The solvents are sufficiently lipophilic to dissolve the medicine, and on the other hand, are adequately hydrophilic to provide the desired active agent transport through the skin (col.2, lines 46-49).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a transdermal therapeutic system comprising a polymer layer comprising polysiloxane and microreservoirs containing the active substance and a solvent as disclosed by WO '138, and replace the solvent disclosed by the WO '138 by any of the solvents disclosed by US '657 because the solvents disclosed by US '657 are sufficiently lipophilic to dissolve the medicine, and on the other hand, are adequately hydrophilic to provide the desired active agent transport through the skin, with reasonable expectation of having a transdermal therapeutic system with dissolved active substances ready to transport across the skin with success.

7. Claims 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO '138 in view of US '657 as applied to claims 1, and 3-10 above, and further in view of US 5,145,682 ('682).

WO '138, as discussed above, teaches a transdermal absorption dosage unit comprising backing layer, a layer of polysiloxane polymer matrix in which a drug is

microdispersed; an adhesive means for securing the dosage unit to the skin of the treated subject; and a release liner, wherein the active substance is in the dissolved form. The reference also disclosed a process for the manufacture of the TTS. US '657 teaches the ambiphilic solvents.

The references in combination, however, do not teach the polysiloxane polymer to be amine-resistant (claim 2).

US '682 disclosed a transdermal absorption dosage unit comprising an impervious backing; an adhesive polymer layer of silicone adhesive comprising miccroreservoirs encapsulating the active substance; additional adhesive layer; a releasable protective film layer (abstract; col.3, lines 118-19, 56; col.7, lines 30-31). Amine-resistant adhesive polymers are suitable for use in making the adhesive polymer layer such as BIO-PSA, used by applicant in their examples, because they are biologically acceptable and chemically compatible with the pharmaceutical substances (col.6, lines 40-64).

Accordingly, it would have been obvious to one having ordinary skill in the art at the time of the invention to provide a transdermal therapeutic system comprising a polymer layer comprising polysiloxane and microreservoirs containing the active substance and an ambiphilic solvent as disclosed by WO '138 in view of US '657, and replace the polysiloxane by the amine-resistant polysiloxane as taught by the US '682 because US '682 teaches that the amine resistant polysiloxane are biologically acceptable and chemically compatible with the pharmaceutical substances with

reasonable expectation of having a safe transdermal therapeutic system with dissolved active substances ready to transport across the skin with success.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Isis Ghali whose telephone number is (703) 305-4048. The examiner can normally be reached on Monday through Thursday from 7:00 AM to 5:30 PM, Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K. Page, can be reached on (703) 308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3592.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Isis Ghali
Examiner
Art Unit 1615

Isis Ghali
05/05/03